IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Caspofungin 50mg powder for concentrate for solution for infusion
Caspofungin
PA0281/246/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number DE/H/4672/001-002/DC with the DE as RMS. The responsibility of RMS was transferred to UK/H/6888/1-2/DC and again to Ireland on 02/07/2018 under procedure number IE/H/0667/1-2/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA0281/246/001-002
Marketing Authorisation Holder: Pinewood Laboratories Ltd

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The DE public assessment report published at the time of the initial marketing authorisation is provided herein.

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the applications for *Caspofungin Wockhardt* and *Caspofungin Inresa 50 / 70 mg Pulver für ein Konzentrat zur Herstellung einer Infusionslösung* indicated for:

- Treatment of invasive candidiasis in adult or paediatric patients.
- Treatment of invasive aspergillosis in adult or paediatric patients who are refractory to or intolerant of amphotericin B, lipid formulations of amphotericin B and/or itraconazole. Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy.
- Empirical therapy for presumed fungal infections (such as Candida or Aspergillus) in febrile, neutropenic adult or paediatric patients

are approved.

II. EXECUTIVE SUMMARY

II.1 Problem statement

For generic application this section is not applicable.

II.2 About the product

These applications are submitted as a Decentralised Procedure for caspofungin 50mg/ml and 70mg/ml powder for concentrate for solution for infusion and are based on Art 10(1) (generic application) of Directive 2001/83/EC (as amended).

The pharmacotherapeutic classification for caspofungin acetate is J02AX04; antimycotics for systemic use.
Caspofungin acetate is a semi-synthetic lipopeptide that belongs to the class of antifungal agents called the echinocandin family. Caspofungin blocks, through non-competitive inhibition of the enzyme β(1,3)-D-glucan synthase, the synthesis of the fungal cell wall component β(1,3)-D-glucan which is essential for the cell wall synthesis of numerous fungal species and yeasts, but is absent in mammalian cells.
Fungicidal activity with caspofungin has been demonstrated against a range of *Candida* and *Aspergillus* species.

Caspofungin 50 mg and 70 mg powder for concentrate for solution for infusion is indicated for the:

- Treatment of invasive candidiasis in adult or paediatric patients.
- Treatment of invasive aspergillosis in adult or paediatric patients who are refractory to or intolerant of amphotericin B, lipid formulations of amphotericin B and/or itraconazole. Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy.
- Empirical therapy for presumed fungal infections (such as Candida or Aspergillus) in febrile, neutropenic adult or paediatric patients

In adults a single 70 mg loading dose should be administered on Day-1, followed by 50 mg daily thereafter. In patients weighing more than 80 kg, after the initial 70 mg loading dose, caspofungin 70 mg daily is recommended. No dosage adjustment is necessary based on gender or race.
In paediatric patients (12 months to 17 years of age), dosing should be based on the patient's body surface area. For all indications, a single 70-mg/m^2 loading dose (not to exceed an actual dose of 70 mg) should be administered on Day 1, followed by 50 mg/m^2 daily thereafter (not to exceed an actual dose of 70 mg daily).
The safety and efficacy of caspofungin have not been sufficiently studied in clinical trials involving neonates and infants below 12 months of age. Caution is advised when treating this age group.

II.3 General comments on the submitted dossier

The active substance is not considered a new active substance.

These decentralised applications concern a generic version of caspofungin acetate, under the trade names

- Caspofungin Wockhardt 50 mg and 70 mg powder for concentrate for solution for infusion (= DE/H/4672/001-002/DC)

and

- Caspofungin Inresa 50 mg and 70 mg powder for concentrate for solution for infusion (=DE/H/4794/001-002/DC)

and are based on Art. 10(1) as generic application of Directive 2001/83/EC (as amended).
All products, Caspofungin Wockhardt 50 mg/70 mg and Caspofungin Inresa 50 mg/70 mg, are identical products but with different applicants and CMS.

The originator product is Cancidas® 50 mg and 70 mg powder for concentrate for solution for infusion (Merck Sharp & Dohme Limited, UK), which was granted marketing authorisation in EU through a centralised procedure on October 24th, 2001 (EU/1/01/196/001-002).

With DE as the Reference Member State in this Decentralized Procedure, Wockhardt UK Ltd., Great Britain is applying for the Marketing Authorisations for Caspofungin Wockhardt 50 mg and 70 mg powder for concentrate for solution for infusion in IE and UK.
With DE as the Reference Member State in this Decentralized Procedure, Inresa Arzneimittel GmbH, Germany is applying for the Marketing Authorisations for Caspofungin Inresa 50 mg and 70 mg powder for concentrate for solution for infusion in IE and UK.

A Scientific Advice was given by Germany on 16th of April 2015.

It should be noted, that these decentralized applications are identical to the ongoing decentralized application DE/H/4555/001-002/DC for Caspofungin Diamed 50 mg and 70 mg powder for concentrate for solution for infusion applied by DiaMed Beratungsgesellschaft für pharmazeutische Unternehmen mbH with ES, FR, IT, and UK as CMS.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

Drug Product

GMP compliance at the manufacturer involved in the production of the drug product for the applied manufacturing operations has been adequately demonstrated by GMP Certificate and Manufacturer's.

Drug Substance

Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU. The declaration covers the redefined starting material.

II. QUALITY ASPECTS

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

Caspofungin acetate is a semi-synthetic lipopeptide. Caspofungin acetate is not described in the European Pharmacopoeia. Caspofungin acetate possesses 16 stereo centres.
The active substance documentation is supplied by the ASMF procedure. Caspofungin acetate is a semi-synthesis product. The starting material is defined as the cells from which the fermentation product KB0 is produced. The intermediate KB0 is a fermentation product.
The proposed retest period is 24 months when stored in well closed container at temperature not more than -70°C.

Drug Product

The drug product is a powder for concentrate for solutions for infusion filled in colourless glass vials, closed with a grey bromobutyl rubber stopper, and sealed with a flip-off seal with plastic cap. There are two strengths of the product; 50 mg/vial and 70 mg/vial. They are proposed for approval as generic drug according to Article 10.1, Directive 2001/83 EC. The reference drug product is Cancidas® – Merck Sharp & Dohme Limited.

The development of the product has been done in line with the product of reference. The drug products contain the same drug substance in the same form and concentration and the same excipients as the European innovator products.

The manufacturing process contains of weighing, preparation of the intermediate product, sterile filtration, filling, semi-stoppering, lyophilization, and sealing of the vials.

The release and shelf-life specification contain specifications for the following parameters: Appearance, identification, reconstitution time, appearance after reconstitution (clarity and coloration of solution), pH after reconstitution, water, uniformity of dosage unit, particulate contamination (after reconstitution), related substances, sterility, bacterial endotoxins, and assay.

The requested shelf life is 18 months with the recommendation for storage "Store in a refrigerator 2°C - 8°C.".

III. NON-CLINICAL ASPECTS

III.2 Non-clinical aspects

There are no objections to approval of Caspofungin 50/70 mg powder for concentrate for solution for infusion from a non-clinical point of view.

Environmental Risk Assessment (ERA)

Since Caspofungin 50/70 mg powder for concentrate for solution for infusion is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

III.3 Clinical aspects

The clinical overview refers to 120 publications up to year 2014. The overview is satisfactory.

Caspofungin Diamed / Caspofungin Wockhardt / Caspofungin Inresa 50 mg and 70-mg powder for concentrate for solution for infusion is indicated for parenteral use only. No bioequivalence studies are required for this type of product according to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) and the applicant submitted none.

Pharmacokinetics

Caspofungin is extensively bound to albumin. The unbound fraction of caspofungin in plasma varies from 3.5 % in healthy volunteers to 7.6 % in patients with invasive candidiasis. Distribution plays the prominent role in caspofungin plasma pharmacokinetics and is the rate-controlling step in both the alpha- and beta-disposition phases. The distribution into tissues peaked at 1.5 to 2 days after dosing when 92 % of the dose was distributed into tissues.

Caspofungin undergoes spontaneous degradation to an open ring compound. Further metabolism involves peptide hydrolysis and N-acetylation. Two intermediate products, formed during the degradation of caspofungin to this open ring compound, form covalent adducts to plasma proteins resulting in a low-level, irreversible binding to plasma proteins.

In vitro studies show that caspofungin is not an inhibitor of cytochrome P450 enzymes 1A2, 2A6, 2C9, 2C19, 2D6, or 3A4. In clinical studies, caspofungin did not induce or inhibit the CYP3A4 metabolism of other medicinal products. Caspofungin is not a substrate for P-glycoprotein and is a poor substrate for cytochrome P450 enzymes.

The elimination of caspofungin from plasma is slow with a clearance of 10-12 ml/min. Plasma concentrations of caspofungin decline in a polyphasic manner following single 1-hour intravenous infusions. A short alpha-phase occurs immediately post-infusion, followed by a beta-phase with a half-life of 9 to 11 hours. An additional gamma-phase also occurs with a half-life of 45 hours. Distribution, rather than excretion or biotransformation, is the dominant mechanism influencing plasma clearance.

Approximately 75 % of a radioactive dose was recovered during 27 days: 41 % in urine and 34 % in faeces. There is little excretion or biotransformation of caspofungin during the first 30 hours after administration. Excretion is slow and the terminal half-life of radioactivity was 12 to 15 days.

A small amount of caspofungin is excreted unchanged in urine (approximately 1.4 % of dose). Caspofungin displays moderate non-linear pharmacokinetics with increased accumulation as the dose is increased, and a dose dependency in the time to reach steady state upon multiple-dose administration.

Pharmacodynamics
The pharmacodynamic properties of caspofungin have been demonstrated for the reference product and are adequately described in the relevant section of the submitted SmPC.

Clinical efficacy
This application concerns a generic version of caspofungin powder for concentrate for solution for infusion. No new clinical studies on efficacy are necessary.

Legal Status
For prescription only

User Testing
A user testing was performed for Caspofungin Diamed* 70 mg powder for concentrate for solution for infusion. The results indicate that the final version of the submitted PI can be considered as user friendly.
Regarding the Caspofungin Diamed 50 mg powder for concentrate for solution for infusion, the applicant provided a bridging report. The bridging has been justified by the applicant.

Note:*
The user test was submitted with the ongoing decentralized procedure DE/H/4555/002/DC for the caspofungin 'Caspofungin Diamed 70 mg', which is identical to the caspofungin products as applied for in these applications.
Test results indicate that the patient information leaflet is well structured and organized, easy to understand and written in a comprehensible manner. The test shows that the leaflet is readable and patients/users are able to act upon the information that it contains. This means that the package leaflet is fully compliant with Directive 2001/83/EC as amended by Directive 2004/27/EC and Guideline on the Readability. Based on the above mentioned information the package leaflet can be evaluated as acceptable.

Summary Pharmacovigilance system
The Applicant has submitted a signed Summary of the Applicant's and/or Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan
The Applicant has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to caspofungin.

Summary table of safety concerns as proposed and approved in RMP:

Important identified risks	• Hepatotoxicity • Hypersensitivity reactions (including histamine-mediated allergic reactions) • Drug resistance • Drug-drug interaction: Rifampin and other inducers of drug clearance • Drug-drug interaction: Cyclosporine A • Drug-drug interaction: Tacrolimus
Important potential risks	None

Missing information	• Exposure during pregnancy • Additional data on the safety and effectiveness in neonates and infants <3 months of age

There are no ongoing or planned studies in the pharmacovigilance plan and no additional risk minimisation measures proposed which is acceptable.

The RMP is approved.

The Applicant shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)-
With regard to PSUR submission, the MAH should take the following into account:
- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

V. OVERALL CONCLUSIONS

IV. BENEFIT RISK ASSESSMENT

The applications contain an adequate review of published non-clinical and clinical data.
The pharmacology, pharmacokinetics and toxicology of the active substance are sufficiently known.
Bioequivalence studies are not necessary in view that the reference product and the proposed products are aqueous intravenous solution and the quantitative and qualitative composition is similar between the innovator and proposed products. The sought indications are similar to those approved in Germany for the market leader.
From the quality, clinical and non-clinical point of view, there are no objections to approval of the medicinal products as applied for. Thus the benefit/risk balance of these generic caspofungin formulations *Caspofungin Wockhardt / Caspofungin Inresa 50 / 70 mg Pulver für ein Konzentrat zur Herstellung einer Infusionslösung* can be considered similar to that of the reference product.
The benefit/risk assessment is considered positive.
The application is approved. For intermediate amendments see current product information.

VI. REVISION DATE

15/03/2022

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From DE/H/4672 to UK/H/6888			
RMS transfer	From UK/H/6888 to IE/H/667			
MAH transfer				31/12/2022